

Talk

GATA4 Transcription Factor and Hypoxia Inducible Factor 2 α in Liver Fibrosis Disease



Noelia Arroyo de Alba(1) y Anabel Rojas(1,*)

(1)Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Avda. Americo Vesputio s/n. Parque Científico y Tecnológico Cartuja, 41092, Sevilla, España.

(*)Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM).

Keywords: HIF2 α ;GATA4; hepatic stellate cells; liver fibrosis

ABSTRACT

Motivation: Liver fibrosis, and cirrhosis, is a disease with a high incidence in the population, causing around 1.8% of global mortality (1). Upon liver injury, mainly caused by alcohol abuse, hepatitis virus infection or congenital bile duct obstruction, quiescent hepatic stellate (HSCs) become activated. HSCs are mesenchymal cells that are located between the hepatocytes in the Disse space. Active HSCs are the main source of extracellular component of the matrix (ECM), including collagen that forms the scars in a fibrotic liver (2). Reversion of active HSCs to a quiescent state is currently one of the emerging strategies for liver fibrosis therapy. However, the molecular mechanisms underlying activation /reversion of HSCs remains unknown. Previous studies from the host lab have uncovers a role of GATA4 transcription factor as a negative regulator of the activation of HSCs (3). Moreover, the expression of GATA4 in LX2, a human-derived hepatic stellate cell line, decreased the levels of fibrotic markers. Interestingly a gene profile analysis of LX2 overexpressing GATA4 revealed an downregulation of Hypoxia Inducible Factor 2 α , HIF2 α .

In this project we aim to study the role of HIF2 α in the phenotype of HSCs. To this aim, we will mouse model and LX2 cell line.

Methods: Using a mouse line to conditionally stabilize HIF2 α protein in HSCs, we have analyzed the impact of HIF2 α in the development of liver fibrosis. We have characterized the mouse livers by immunohistochemistry, immunofluorescence and qPCR to evaluate the expression of fibrotic markers. Additionally, we are using previously established inhibitors of HIF2 α to analyze the loss of HIF2 α in the phenotype of active LX2 cells.

Results: Our data shows that stabilization of HIF2 α in HSCs leads to induction of liver fibrosis in mice, with accumulation of fibrotic markers such as collagen, laminin and smooth muscle alpha actin, and a decrease in cell proliferation. The effectiveness of HIF2 α inhibitors in LX2 is still under study.

Conclusions:The results obtained clearly shows a relationship between GATA4 and HIF2 α in the induction of liver fibrosis. The maintenance of HSCs quiescence by GATA4 might be exerted, at least in part, by inactivating HIF2 α expression. The activation of HIF2 α ultimately leads to activation of HSCs and therefore to the induction of liver fibrosis. Studies of loss of function by using HIF2 α inhibitors will reinforce the importance of HIF2 α in the regulation of HSCs phenotype.

REFERENCES

1. Battaller, R. and Brenner, D.A. (2005) Liver fibrosis. J. Clin. Invest., 115, 209-218.
1. Gordillo, M. et al. (2015) Orchestrating liver development. Development. 142, 2094-2108
3. Delgado, I. et al. (2014) GATA4 loss on the septum transversum mesenchyme promotes liver fibrosis in mice. Hepatology, 59, 2358-2370. doi: 10.1002/hep.27005..